Case Reports

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An overlooked cause of hepatitis and thrombocytopenia with clinico-biochemical discrepancy: A case of infectious mononucleosis

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ABSTRACT

Objectives: A 22-year-old male was admitted to the outpatient clinic with fatigue, fever, and a sore throat. High transaminase levels, moderate thrombocytopenia, and elevated acute phase reactants were detected ten times. Ultrasound imaging revealed hepatosplenomegaly and a peripheral blood smear showed Downey cells. Epstein-Barr virus (EBV) infection was considered the definite diagnosis, and EBV serology was performed. His mild clinic improved to normal within days, but the patient's clinical progression and laboratory findings were incompatible. Laboratory results were on the extreme side, while the clinic was mildly deteriorating. EBV viral capsid antigen IgM was high, supporting the initial diagnosis. Biochemical normalization followed clinical improvement many days later. Clinicians should know that EBV infection may be mild, while laboratory results illustrate extreme findings.

Keywords: Epstein Barr virus, aminotransferase, thrombocytopenia, hepatomegaly, splenomegaly

Epstein-Barr (EBV) is a herpes virus that spreads through close contact between susceptible individuals and asymptomatic EBV carriers. While most cases are subclinical, symptomatic patients may have fever, lymphadenopathy, and tonsillopharyngitis, which are included in the classic triad. There may also be atypical cases presenting with ascites, arthritis, and severe abdominal pain.[1] Nearly 95% of adults worldwide are infected with EBV.[2] Hepatitis is a common feature of EBV infection, with 80-90% of cases demonstrating a mild to moderate and temporary rise of liver enzymes. Severe hepatocellular liver injury is rare.

Nevertheless, half of the fatal infectious mononucleosis cases have been reported as the result of liver failure.[3] An alteration in white blood cells is the most prominent hematological feature in primary EBV infection, giving the disease its name (infectious mononucleosis). Additional hematological disturbances, including mild thrombocytopenia, are less pronounced, although usually encountered.[4]

CASE PRESENTATION

A 22-year-old male was referred to our tertiary care general internal medicine clinic from a primary care center, where he was admitted with a sore throat and fever due to a low platelet count (88.000 cells/μL). He states that his fever and sore throat have subsid-

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Table 1. Results of the initial laboratory and imaging studies

Parameter	Results	Reference Range
Hemoglobin (g/dL)	15,7	13,5-18
Leukocyte (x10^3/µL)	9.61	4.5 – 11
Platelet (x10^3/µL)	94	150 – 400
Lymphocyte (x10^3/µL)	4.76	1 – 4
Monocyte (x10^3/µL)	1.74	0 – 1
CRP (mg/L)	42.2	0 – 5
Sedimentation Rate (mm/hour)	12	0 – 20
Ferritin (µg/L)	1273	21 – 274
Total Bilirubin (mg/dL)	1.00	0.3 – 1.2
Direct Bilirubin (mg/dL)	0.54	0 – 0.5
AST (U/L)	127	0.3 – 1.2
ALT (U/L)	182	0 – 0.5
ALP (U/L)	293	50 – 116
GGT (U/L)	518	< 55
Abdomen US	The liver measured 175 mm, the spleen measured 155 mm, and other findings were normal.	

ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, GGT: Gamma-glutamyltransferase, US:ultrasonogrophrapy

ed, but now he reports left-side, left upper quadrant pain that worsens with breathing. He reports no prior diseases. He is a regular smoker and reported binge drinking four days ago. His physical examination was unrevealing and showed typical vital signs. On physical examination, no lymph nodes other than a normal-sized, unremarkable lymph node in the suboccipital region were palpated. The respiratory examination was unrevealing. On abdominal examination, there were no palpable liver, spleen, or mass, and palpation was unremarkable. Basic laboratory tests, viral hepatitis markers, peripheral blood smear, chest radiography, and upper abdominal ultrasonography (US) were ordered. The results revealed elevated white blood cells predominately in lymphocytes and monocytes, moderate thrombocytopenia, elevated acute phase re-

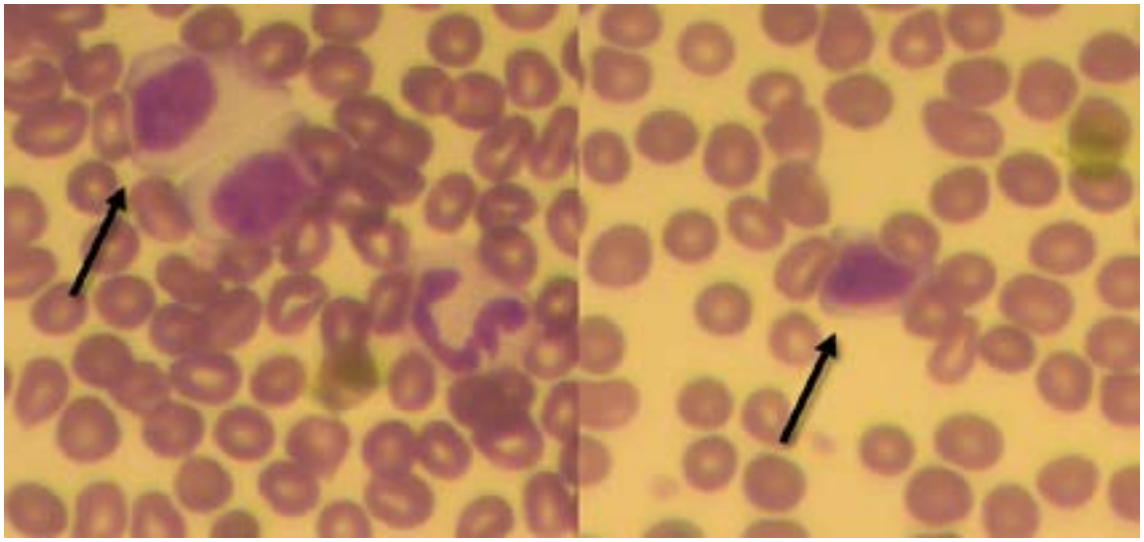

Fig. 1. Reactive lymphocytes (Downey cells) in peripheral blood smear (x400)

Table 2. Results of the control laboratory studies at day 3

Parameter	Results	Reference Range
Hemoglobin (g/dL)	15,4	13,5-18
Leukocyte (x10^3/µL)	15.7	4.5 – 11
Platelet (x10^3/µL)	126	150 – 400
Lymphocyte (x10^3/µL)	11.4	1 – 4
Monocyte (x10^3/µL)	1.41	0 – 1
CRP (mg/L)	28,1	0 – 5
Total Bilirubin (mg/dL)	1,20	0.3 – 1.2
Direct Bilirubin (mg/dL)	0,84	0 – 0.5
AST (U/L)	267	0.3 – 1.2
ALT (U/L)	413	0 – 0.5
ALP (U/L)	435	50 – 116
GGT (U/L)	714	< 55

ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, GGT: Gamma-glutamyltransferase

actants, and 2-3 times higher elevations of transaminases and cholestatic enzymes. Initial laboratory and radiology results were presented in Table 1 in detail. Multiple reactive lymphocytes (i.e., Downey cells) were observed in the peripheral smear, as illustrated in figure 1. Abdominal US demonstrated splenomegaly and hepatomegaly. The patient's clinical, imaging, blood smear, and laboratory results were consistent with EBV infection; hence, EBV serology was requested, and he was discharged with a follow-up plan. He returned for a follow-up visit three days later with no clinical signs or complaints. Control laboratory tests revealed even more severe lymphocytosis and an up to 10-fold increase in liver transaminases. Control laboratory results were presented in Table 2 in detail. He was assured and sent home with a follow-up plan. A few days later, EBV viral capsid antigen immunoglobulin M (VCA) IgM-2.2 S/CO was detected, and the patient's diagnosis of infectious mononucleosis was confirmed. The patient was advised to take bed rest and avoid taking hepatotoxic drugs, especially alcohol, and NSAIDs, as much as possible. The patient was monitored with close outpatient clinic follow-up. Later in the follow-up, his hematological and liver biochemistry levels returned to normal with no clinical or biochemical abnormalities. Informed consent was obtained from the patient before manuscript submission.

DISCUSSION

We report a case study on a young and healthy male patient with mild upper respiratory infection symptoms. However, the patient also displayed moderate to severe hematological and biochemical abnormalities. Based on the observed discrepancy between clinical manifestations and test findings, the patient under consideration is deemed worthy of reporting.

Epstein-Barr virus (EBV) patients may exhibit clinical manifestations such as splenomegaly, lymphadenopathy, headache, tiredness, fever, and sore throat. Patients can experience symptoms for an extended period, with exhaustion being the most frequently reported persistent symptom. It was noted that around 25% of the patients had physical examination findings such as cervical lymphadenopathy and pharyngitis six months after the first infection.[5]

Given the observation of lymphocytosis and atypical lymphocytes in blood tests, liver function tests may exhibit aberrant elevations. A study conducted by Nahum Méndez-Sánchez *et al*. aimed to elucidate the hepatic symptoms and problems related to Epstein-Barr virus (EBV) infection. The researchers documented a cohort of patients who had liver manifestations concerning EBV infection. Hepatic abnormalities, characterized by increased levels of transaminases and/or bilirubin, were observed in over 77% of the patient population.

In the aforementioned study, the hematological tests revealed that a significant proportion, precisely over 44%, of the patients exhibited concurrent manifestations of one or more symptoms. The study identified cytopenia affecting two distinct cell lines, with leukopenia (defined as a white blood cell count below 4,000 cells/µL) and thrombocytopenia (characterized by a platelet count below 150,000 platelets/µL) being the prevailing hematological abnormalities. However,

our patient exhibited heightened leukocytosis despite the presence of thrombocytopenia.[6]

Ferritin is a positive acute phase reactant, and it has been shown to correlate with disease severity.[7] Recently published case reports also illustrated similar levels of hyperferritinemia due to EBV. Similarly, their case also exhibited hepatitis to the same extent.[8]

Serological assays are the most efficacious diagnostic tools. The heterophile antibody assays detect immunoglobulin M (IgM) antibodies specific to the Epstein-Barr virus (EBV). Although the heterophile antibody test was not available at our clinic and hence was not requested, it is worth noting that this test holds value as an initial diagnostic tool due to its cost-effectiveness, prompt results, and moderate sensitivity ranging from 63% to 84% and high specificity ranging from 84% to 100%. One potential drawback is that heterophile antibodies can be activated by other disease processes, leading to a positive result unrelated to acute Epstein-Barr virus (EBV) infection. Additionally, these antibodies may persist for a duration exceeding one year, further contributing to potential false positive outcomes.[9]

The management of infectious mononucleosis typically involves supportive measures, which are comparable to the approach taken in the treatment of other viral diseases. It is recommended that clinicians guide patients regarding the importance of prioritizing sufficient periods of rest, maintaining proper hydration, and adhering to a well-balanced nutritional regimen. Acetaminophen and nonsteroidal anti-inflammatory medications (NSAIDs) are efficacious in the treatment of pain and malaise when used as required.[10]

In conclusion, EBV infection should be considered in the differential diagnosis of patients presenting with severe hypertransaminasemia, moderate to severe thrombocytopenia, and hyperferritinemia exceeding 1000 µg/L, especially when clinical and laboratory findings do not significantly overlap.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: ATG; Study Design: ATG; Supervision; ATG; Materials: ED; Data Collection and/or Processing: ATG; Analysis and/or Data Interpretation: ATG; Literature Review: ED; Critical Review: ATG; Manuscript preparing: ATG, ED.

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